

REMARKS

Claims 31, 32, 43, 45-47, and 50-55 are pending in the application. Claims 31, 32, 43, 45-47, and 50-55 are under active consideration.

Claims 31, 32, 46, 50, and 52-54 have been variously amended as suggested by the Examiner. Claim 45 has been amended to depend from claim 31 instead of canceled claim 44. The amendments do not narrow the scope of the previously presented claims, but merely involve formalities, grammatical oversights/preferences, typological errors, and the like. These amendments to the claims are made solely to obtain expeditious allowance of the instant application and not for reasons related to patentability.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Entry of the claim amendments is respectfully requested

Applicant notes with appreciation the withdrawal of the previous rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a).

Double Patenting

Claims 31, 32, 43-47, and 50-55 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,638,513. Applicant reiterate the request that the requirement for submission of a Terminal Disclaimer with respect to U.S. Patent No. 6,638,513 be held in abeyance until there is an indication of allowable subject matter in the present application.

35 U.S.C. § 112, first paragraph, New Matter

Claim 31 has been rejected under 35 U.S.C. § 112, first paragraph as allegedly containing new matter. In particular, the Office Action alleges:

It should be noted that the method of producing the glycoconjugate that is described in the instant specification involves replacement of sialic acid residue N-acetyl groups specifically with N-propionyl groups. The method described

herein lacks the instantly recited step (c), i.e., covalently attaching a C₃-C₁₆ long-chain aliphatic lipid to the nonreducing end of the MenB OS obtained in step (b)'. As set forth previously, page 14, line 16 through page 16, line 33 of the instant specification describe methods of preparing glycoconjugates with covalently attached lipids. A further review of the specification indicates that these portions of the specification are limited to a specific MenB OS glycoconjugate, 'CONJ-4', comprising substantially homogeneous sized N-propionylated MenB OS having a C₃-C₁₆ long-chain aliphatic lipid covalently attached to the non-reducing end of the N-propionylated MenB OS and being conjugated to a protein carrier. These portions of the specification do not describe a glycoconjugate as recited in the amended claim 31 comprising MenB OS having N-acetyl groups replaced with 'N-C₃-C₈ acyl groups', as recited currently. (Office Action, page 4.)

Applicant respectfully traverses the rejection.

Applicant draws the Examiner's attention to page 14, lines 14-17 of the present application where it states "further glycoconjugates can be formed from the above-described sized MenB OS derivative fragments. In particular, the presence of the lipid moiety at the reducing ends of bacterial MenB PS has been demonstrated." The "above-described" MenB OS derivative fragments refer, in part, to "C₃-C₈ acyl derivatives [that] can be made by first N-deacylating native MenB (obtained from e.g., *N. meningitidis* cultures) in the presence of a strong base to quantitatively remove N-acetyl groups and to provide a reactive amine group in the sialic acid residue parts of the molecule." Page 11, lines 1-6. Further, "the above-described N-acylated MenB polysaccharide derivatives (i.e. C₃-C₈ acyl derivatives) are fragmented and then size-fractionated to provide a substantially homogenous population of intermediate "sized" MenB oligosaccharide fragments for use in preparing glycoconjugates." Page 11, lines 25-30.

Accordingly, Applicant respectfully contends that the replacement of sialic acid residue N-acetyl groups with N-C₃-C₈ acyl groups on substantially homogenous population of oligosaccharide fragments for use in preparing glycoconjugates with or without a lipid moiety, is adequately described in the application as filed. Covalently attaching a C₃-C₁₆ long-chain aliphatic lipid to the non-reducing end of a MenB OS glycoconjugate is further described on pages 14-18 of the present application. Additional, exemplification of the C₃-C₈ acyl derivatives is provided at page 8, lines 1-11; page 11, lines 1-7; page 13, lines 26-34; and page 16, lines 1-22. In particular, see the reference of

EP 504,202 cited at page 8, lines 10-11, which describes substitution of MenB sialic acid N-acetyl groups with C₄-C₈ acyl groups. As clarified, the preparation of the N-propionyl derivative is described as a preferred embodiment, and not as the only embodiment.

For at least these reasons, withdrawal of the new matter rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

35 U.S.C. § 112, second paragraph

Claims 31, 32, 43, 45-47, and 51-55 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite (Office Action, pages 4-5).

(a) The Office Action alleges that “[c]laims 31 and 32 as amended, have improper antecedent basis in the limitation: ‘the substantially homogeneous sized MenB OS/CRM197 toxoid glycoconjugate’ (see last two lines), because there is no earlier recitation of ‘a substantially homogeneous sized MenB OS/CRM197 toxoid glycoconjugate’ in the claim” (Office Action, page 5). In order to expedite prosecution, Applicant have amended claims 31 and 32 in the preamble to make explicit that the recited glycoconjugates of the claims are substantially homogenous sized.

(b) Claim 50 has been amended similarly.

(c) The Office Action alleges that “[c]laim 32 is confusing and internally inconsistent in the limitation, because the first two lines of the claim indicates that the glycoconjugate produced by the recited method is ‘A *Neisseria meningitidis* serogroup B capsular oligosaccharide (MenB OS) glycoconjugate’. However, the product obtained at the end of step (e) of the method is recited to be ‘the substantially homogenous sized MenB OS/CRM197 toxoid glycoconjugate’. The two glycoconjugate products are not of the same scope” (Office Action, page 5). In order to expedite prosecution, Applicant has amended claim 32 in the preamble to make explicit that the recited glycoconjugate of this claim is a MenB OS/CRM197 toxoid glycoconjugate.

(d) The Office Action alleges that “[i]n step (d) of claims 31 and 32, for proper antecedent basis, it is suggested that Applicant replace the limitation ‘single end-activated MenB OS’ with the limitation --single end-activated MenB OS of said DP--” (Office Action, page 5-6). Applicant previously made these amendments to claims 31 and 32 in the response to the Office Action of March 23, 2005.

(e) The Office Action alleges that “[i]n line 7 of claim 31, line 8 of claim 32, and line 6 of claim 50, for clarity and/or consistency, it is suggested that Applicant replace the limitation ‘of (a)’ with --of step (a)--” (Office Action, page 6). In order to expedite prosecution, Applicant has amended claims 31, 32, and 50, as suggested by the Examiner, to recite “step (a).”

(f) The Office Action alleges that “[f]or clarity, it is suggested that Applicant replace the limitation: ‘the single end-activated MenB OS’ in line 13 of claim 31, and line 14 of claim 32, with --the single end-activated MenB OS obtained in step (d)--” (Office Action, page 6). In order to expedite prosecution, Applicant has amended claims 31 and 32, as suggested by the Examiner, to recite “the single end-activated MenB OS obtained in step (d).”

(g) Claim 50 has been amended similarly to claim 31.

(h) The Office Action alleges that claims 46 and 53, which depend from claim 45 and claim 52 respectively, are not properly further limiting. It is suggested that Applicant replace the limitation ‘wherein the carrier molecule is a nontoxic mutant bacterial toxoid’ with the limitation wherein the bacterial toxoid is a nontoxic mutant bacterial toxoid--” (Office Action, page 6). In order to expedite prosecution, claims 46 and 53 have been amended, as suggested by the Examiner, to recite “wherein the bacterial toxoid is a nontoxic mutant bacterial toxoid.”

(i) The Office Action alleges that “[c]laims 45 and 46 are indefinite and incorrect in their direct or indirect dependency from the canceled claim 44” (Office Action, page 6). Applicant has amended claim 45 to depend from claim 31 instead of canceled claim 44.

(j) The Office Action alleges that “[f]or proper antecedence, in line 1 of claim 52, it is suggested that Applicant replace the limitation ‘the carrier molecule’ with the limitation –the protein carrier molecule--” (Office Action, page 6). In order to expedite prosecution, Applicant has amended claim 52 to recite the “protein carrier molecule.”

(k) The Office Action alleges that “[c]laim 54 is vague and confusing in the limitation: ‘a CRM₁₉₇ carrier molecule’. For the purpose of distinctly claiming the subject matter, it is suggested that Applicant replace the limitation with --CRM₁₉₇--” (Office Action, page 6). In order to expedite prosecution, Applicant has amended claim 54, as suggested by the Examiner, to recite “CRM₁₉₇.”

(l) The Office Action alleges that “[c]laims 43, 45-47 and 51-55, which depend directly or indirectly from claim 31 or claim 50, are also rejected as being indefinite because of the indefiniteness identified above in the base claim” (Office Action, page 6). The rejections are overcome and/or rendered moot by the current amendments to the claims.

For at least the above reasons, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn. Additionally, upon entry of these amendments, Applicant respectfully solicits allowance of claims 31, 32, 43, and 45-47 because there are no other outstanding rejections remaining with respect to those claims.

35 U.S.C. § 103

Claims 50-55 are rejected under 35 U.S.C. § 103 as being unpatentable over the reference of Jennings *et al.* U.S. Patent No. 5,576,002 (Jennings '002) or Jennings *et al.* U.S. Patent No. 5,902,586 (Jennings '586) in view of the references of Kitazume *et al.* (1992) Anal. Biochem. 202:25-34, or Jennings *et al.* (1985) J. Immunol. 134:2651-2657, and Kniskern *et al.* (1991) U.S. Patent No. 5,847,112, Marburg *et al.* U.S. Patent No. 5,623,057, and Jennings *et al.* U.S. Patent No. 5,811,102 (Jennings '102). In particular, the Office Action alleges:

Given the identified need in the art for glycoconjugate vaccines containing well defined starting polysaccharide materials that are amenable to conjugation as taught by Kniskern *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to replace Jennings' ('002 or '586) serogroup B *Neisseria meningitidis* capsular polysaccharide fragments with Jennings' (1985) homogeneous 12 to 18 residue-long or 10-20 residue-long serogroup B *Neisseria meningitidis* capsular oligosaccharides, or Kitazume's serogroup B *Neisseria meningitidis* capsular oligosaccharides of 12 Dp, to produce the glycoconjugate of the instant invention, with a reasonable expectation of success, because: a) Kniskern *et al.* expressly taught that oligosaccharide conjugates of increased solubility, increased filterability, increased purity, reduced molecular weight, reduced polydispersity, and reduced viscosity can be produced using the polysaccharide of *Neisseria meningitidis* B; or b) Marburg *et al.* expressly taught that significantly improved, consistent and chemically defined, T-cell dependent glycoconjugates of high degree of covalency comprising oligosaccharides of reduced molecular size, reduced polydispersity, and reduced viscosity may be derived from serogroup B *Neisseria meningitidis* capsular polysaccharide. One of ordinary skill in the art would have been motivated to produce the N-propionylated serogroup B meningococcal capsular oligosaccharide glycoconjugate comprising oligosaccharides of reduced homogenous size of Dp 10-20, 12-18, or Dp 12 for the expected benefit of accomplishing: a) improved polysaccharide handling during conjugation and post-conjugation removal of free polysaccharide, higher purity/homogeneity lower molecular size polydispersity and essentially unaltered antigenicity of the polysaccharide, all characteristics that contribute significantly to the consistent formation of a highly defined and highly antigenic glycoconjugate product as taught by Marburg *et al.*; or b) advantageously consistent formation of highly chemically defined, more homogeneous,

highly specific, antigenic conjugates of enhanced immunogenicity as taught by Kniskern *et al.* (Office Action, page 10.)

This rejection is respectfully traversed.

Contrary to allegations made in the present Office Action, neither Kitazume *et al.*, Jennings *et al.* (1985), Kniskern *et al.* (1991), Marburg *et al.*, nor Jennings *et al.* ('102) provide motivation to modify the polysaccharides in Jennings ('002 or '586) to arrive at a substantially homogenous sized *Neisseria meningitidis* serogroup B capsular oligosaccharide (MenB OS) glycoconjugate having oligosaccharides with an average Dp between about 10 and 20.

The molecular weight of compositions in Kniskern *et al.* were generally reduced between 2 and 10 fold (see Column 3, lines 63-65), which correspond to a final Dp of 600-1200 repeating units (Column 9-10, Table II). According to the present Office Action, the size reduced polysaccharide fragments in Kniskern *et al.* resulted in "increased solubility, increased filterability, increased purity, reduced molecular weight..." Page 9, 1st Paragraph. Likewise, Marburg *et al.* teaches polysaccharides with 2-10 fold lower molecular size (<1000 Dp) as compared with the crude bacterial culture derived polysaccharide (Column 4, lines 21-23 and 65-67), which according to the Office Action resulted in "improved polysaccharide handling during conjugation and post-conjugation removal of free polysaccharide, higher purity/homogeneity, lower molecular size polydispersity and essentially unaltered antigenicity of the polysaccharide..." Page 9, 2nd paragraph.

Similarly, in Jennings *et al.* ('002 or '586) "[p]rior to the N-deacetylation procedure, the native polysaccharide has an average molecular weight in the region of about 500,000 to 800,000 Daltons. As a result of N-deacetylation, fragments of the polysaccharide are produced having an average molecular weight ranging from about 10,000 to about 50,000 Daltons (i.e. 10-80 fold reduction in size)." Jennings *et al.* ('002), Column 3, line 64-67. Subsequently, "the resultant N-acylated or N-propionylated glycoconjugates have improved immunogenicity, do not possess significant cross-linking, are soluble in aqueous solutions and are good candidates for vaccine use (see column 5,

lines 5-13 and 35-39).” *Citing* Page 8, 1st paragraph of the present Office Action; *also see* Jennings ‘002 (stating “it is preferred, according to the present invention, to select, for conjugation purposes, the N-acylated material having an average molecular weight corresponding to about 30 to 200 sialic acid residues”) Column 4, line 18-21.

The amount of polysaccharide molecular weight reduction described in Kniskern *et al.* and Marburg *et al.* is less than the molecular weight reduction performed on the compositions in Jennings *et al.* (‘002 or ‘586). Therefore, irrespective of the prior existence of shorter MenB oligosaccharides, neither Kniskern *et al.* nor Marburg *et al.* provide motivation to reduce the size of the already fragmented polysaccharides in Jennings *et al.* (‘002 or ‘586), especially to the specific range cited in the present claims. The only basis on which that argument can be founded involves hindsight reconstruction. Furthermore, the types of improvements made by way of fragmentation in Kniskern *et al.* and Marburg *et al.* are already cited by the current Office Action as being present in the compositions in Jennings *et al.* (‘002 or ‘586). Therefore, Kniskern *et al.* and Marburg *et al.* provide nothing, by way of motivation, to support further depolymerization of the compositions in Jennings *et al.* (‘002 or ‘586). More likely, Kniskern *et al.* and Marburg *et al.* provide motivation to select for the higher molecular weight polysaccharide fragments described in Jennings *et al.* (‘002 or ‘586). On the other hand, if one were to follow the rule articulated in the present Office Action (i.e. smaller is necessarily better), the natural outcome would be to select for individual saccharide units, not an average Dp of about 10-20.

Furthermore, Kniskern *et al.* and Marburg *et al.* are both drawn to *Streptococcus Pneumoniae* polysaccharides as opposed to N-acylated Men. B. glycoconjugates. A more relevant reference by Jennings describes studies with N-Propionylated Group B Meningococcal Polysaccharides (NPrGBMP) and states that “the choice of an 11-kD fragment (for use in the development of a conjugate vaccine against group B meningococcal meningitis) was based on the fact that mouse polyclonal antisera induced by this vaccine, rather than others synthesized using longer or shorter lengths of NPrGBMP, was optimal in terms of bactericidal activity.” J. Exp. Med. 185(11), 1997 1929-38. Subsequently, the fact that there existed Men. B oligosaccharides having a Dp

of 1-9 or up to 18 (as in Jennings *et al.*, 1985), or a Dp of 1-10 or 1-14 (Kitazume *et al.*) does not motivate one to use them in the production of substantially homogenous sized MenB OS glycoconjugates wherein sialic acid residue N-acetyl groups are replaced with N-C₃-C₈ acyl groups, as presently claimed, especially when Jennings himself teaches away from their use in this application.

“An examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. The United States Court of Appeals for the Federal Circuit, our reviewing court, however, has stated that “the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references.” *Ecolchem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, (2000).

Applicant respectfully contends that references cited in the present Office Action fail to provide sufficient teaching or motivation to modify compositions in Jennings ('002 or '586) and arrive at the presently claimed invention. Accordingly, the rejection under 35 U.S.C. § 103 should be withdrawn.

REQUEST FOR INTERVIEW

With exception to a Notice of Allowance, Applicant requests an interview with the Examiner prior to issuance of the next Office Action.


CONCLUSION

In light of the claim amendments and above remarks, Applicant submit that the present application is in condition for allowance. Early notice to that effect is earnestly solicited.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to **Deposit Account No. 03-1664.**

Respectfully submitted,

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